REMARKS

Claims 1-9 are pending and under examination in the application. The specification has been amended to replace the phrase "Figure 6" with "Figure 4" in order to correct a typographical error. Support for the amendment can be found throughout the specification, for example at page 54, lines 17-19, and Figure 4. In addition, the specification has been amended to add sequence identification numbers to the tables on page 53 and 54 to correct a formality, as requested by the Examiner. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Applicants have set forth above the amendments to the specification in clean form as required under 37 C.F.R. § 1.121 (c)(i). Applicants also attach Appendix A with the marked amendments to the specification indicated with brackets and underlining as required under 37 C.F.R. § 1.121 (c)(ii).

Objection to the specification

The specification has been objected to for containing sequence disclosures that lack the notations of "SEQ. ID NO. ___" next to the sequences. In particular, the Office Action cites the table on pages 53-54. Applicants have amended the specification to include the "SEQ. ID NO." notation for the sequences on pages 53-54. The sequence identification numbers correlate to the sequence listing filed with the application on April 20, 2001. Accordingly, Applicants respectfully request

that this ground of objection to the specification be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-9 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. The Office Action alleges that phases such as "collective receptor variant population," "binding activity," and "optimal binding affinity" are defined very broadly.

Applicants submit that the specification provides sufficient description and guidance to convey to one skilled in the art the meaning of the terms recited in the claims. The specification teaches that "collective" refers to an aggregate of members that form the population or sub-population (page 10, lines 19-22). In addition, the specification teaches that a "population" refers to a group of two or more different molecules (page 9, line 26, through page 10, line 11). The term "receptor" is defined on page 5, lines 28-30, to be a molecule of sufficient size so as to be capable of selectively binding a ligand. The specification goes on to teach the physical properties of receptors, for example, at page 5, line 30, to page 6, line 11. In addition, the specification teaches several examples of receptors including binding domains of antibodies and cell surface receptors such as G-protein coupled receptors (see, for

example, page 6, lines 11-17; page 7, lines 4-16; and page 17, line 5, to page 18, line 27).

The specification teaches that a "variant" when used in reference to a receptor is a molecule that shares a similar structure and function (page 8, lines 26-28). For example, variants can possess substantially the same or similar binding function as the parent molecule although variants can have detectable differences in chemical functional groups (page 8, line 31, through page 9, line 2). Variants are described as being directly modified such as by the mutation of an amino acid residue or the addition of a chemical moiety, or indirectly modified such as by the binding of a regulatory molecule or allosteric effector (page 9, lines 3-8). Additional examples of variants are also described, such as an isoform or family member that is distinct but related to the parent (page 9, lines 9-25).

Applicants submit that the specification provides sufficient description and guidance to convey to one skilled in the art the meaning of a "collective receptor variant population." For example, the specification teaches types of variations of a parent receptor that can be used in a collective receptor variant population (page 8, line 26, to page 9, line 25). An example of a polypeptide receptor variant is described in the specification, for example, as differing by one or more amino acids in a functional binding domain (page 9, lines 16-25). Further description of what constitutes relatedness of a receptor variant, including specific amino acid substitutions, is given on page 15, lines 1-24. Thus, a collective receptor variant

population has structural and functional features based on a particular parent ligand.

Although not required, the specification also provides a specific working example of a collective receptor variant population in Example V (page 49, line 3, to page 55, line 15). In Example V, a BR96 antibody is designated as a parent receptor and used as the basis for generating a collective receptor variant population. Six receptor variants were generated using random codon synthesis (see Figure 4 and the table on page 53 and 54). A population of anti-idiotypic antibodies are designated as ligands in this example. Therefore, in addition to teaching the characteristics of a collective receptor variant population, the specification also provides an example of a population of molecules that can be a collective receptor variant population.

Further, the specification provides teaching regarding the use of a collective receptor variant population to provide an expanded receptor target range compared to a single receptor of similar function for the identification of binding ligands (see, for example, page 11, line 20, to page 12, line 20). Several advantages of using a receptor variant population are described in the specification, for example, at page 13, line 1 to page 14, line 11.

Regarding the terms "binding activity" and "optimal binding affinity," Applicants submit that the specification teaches and exemplifies binding activity and optimal binding. For example, the specification discloses a working example

showing binding of anti-idiotypic antibody ligands to BR96 antibody receptor variants using an ELISA assay in Example V and Figure 3 (see page 51, lines 6-16). In addition, as described in Example III, receptor-ligand binding can have multiple molecular interactions which can be used to determine optimal binding (see page 43, line 29, to page 46, line 6). The identification of an optimal binding ligand is exemplified, for example, in Figure 2. Furthermore, the specification teaches that "optimal binding" is a preferred binding characteristic of a ligand and receptor interaction, and can be ligand-receptor interactions of a desired affinity, avidity or specificity (page 10, lines 23-27). Exemplary optimal binding characteristics such as binding affinity, binding to the largest number of variants or binding to greater than some threshold number of variants are also provided in the specification, for example, at page 10, line 27, through page 11, line 14.

In summary, Applicants submit that the specification provides sufficient description and guidance for the meaning of the terms "collective receptor variant population," "binding activity," and "optimal binding activity" as recited in the claims.

The Office Action further alleges that the specification discloses limited and mostly prophetic examples of carrying out the claimed method. Although working examples are not required, Applicants submit that the working example taught in the specification (Example V) describing a method for determining binding of a receptor to one or more ligands by

contacting a collective receptor variant population with one or more ligands and detecting binding of the one or more ligands to the collective receptor variant population provides sufficient description and guidance for the claimed methods.

The Office Action also alleges that there is not adequate description of producing receptors by recombinant expression in melanophore cells as stated in claims 6 and 7 or tagging with an identifiable tag as stated in claim 9. Applicants submit that the specification provides sufficient description to teach one skilled in the art how to recombinantly express a receptor variant population in cells (claim 6) and specifically in melanophore cells (claim 7). In particular, the specification teaches methods of using melanophore cells to express variant receptor populations (page 25, lines 8-32; and Example I, page 37, line 12, through page 40, line 32). For example, the specification teaches specific procedures for deriving melanophore cells (page 37, line 15, to page 38, line 5) and transfecting DNA constructs into melanophore cells (page 39, lines 1-10). Furthermore, producing receptors by recombinant expression in melanophore cells was well known in the art and is described, for example, by Lerner et al. in U.S. Patent No. 5,462,856 which was cited by the Examiner (see, for example, column 13, line 18, to column 14, line 67, provided herewith as Exhibit A). Accordingly, Applicants respectfully submit that the specification provides sufficient description for how to produce receptors in melanophore cells.

In regard to tagging ligands, the specification teaches methods of tagging variants at page 28, line 28, to page 30, line 24. For example, the specification teaches that a large number of tags can be generated with a limited number of different peptides and antibodies specific for those peptides (page 29, lines 30-32). In addition, the specification gives an example of the use of 32 different peptides to generate 4096 different tags (page 30, lines 1-4). Furthermore, the specification teaches methods for detecting the tag, for example, using antibodies specific for the peptides in FACS analysis (page 30, lines 8-20). Moreover, the specification provides an example, Example I, where a variant receptor population is tagged by co-expression of a peptide tag on the parental expression vector (page 38, lines 18-33).

Applicants respectfully submit that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. Therefore, Applicants respectfully request that these grounds of rejection be withdrawn.

Claims 1 and 9 also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Office Action alleges that the claims and nature of the invention regarding receptors and ligands are broad. Applicants respectfully submit that the specification provides sufficient description and guidance to enable all of the claimed methods.

Regarding the alleged breadth of the claims, the specification teaches properties of a receptor and ligand, for example, that a receptor selectively binds to a ligand (page 5, lines 28, to page 6, line 17). In addition, as described above, the specification provides sufficient description and examples of various types of receptors and ligands. Furthermore, a specific working example of receptors and ligands is shown in Example V, where the BR96 antibody is designated as a parent receptor and anti-idiotypic antibodies are ligands (page 49, lines 8-9, and page 50, lines 29-33). Thus, based on the teachings in the specification, one skilled in the art would have readily understood that the claimed receptors and ligands are binding partners having specific binding activity.

Regarding the alleged unpredictability in the art, Applicants respectfully submit that the specification provides sufficient description and guidance to enable the invention as claimed. The Office Action acknowledges that ligand/receptor binding pairs were well-known in the art at the time of the invention, however the Office Action alleges that only limited numbers of such pairs were known. Applicants submit that a number of ligand/receptor binding pairs were known in the art at the time of filing of the application, thus contributing to predictability in the art. For example, attached herewith as Exhibit B is a review article by Power and Wells describing a number of chemokine receptors, which are G-protein coupled receptors, and their corresponding ligands (Trends in Pharm. Sci., 17:209-212 (1996), see in particular page 211, Table 1, exemplifying 10 receptor/ligand pairs). In addition, attached

herewith as Exhibit C is a review article by Bazzoni and Beutler describing several TNF receptor and ligand pairs (N. Engl. J. Med. 334:1717-1725 (1996), see in particular page 1719, Table 1, exemplifying 10 receptor/ligand pairs). Furthermore, attached herewith as Exhibit D is a review article by Fantl et al. describing several receptor tyrosine kinases and corresponding ligands (Annu. Rev. Biochem. 62:453-481 (1993), see in particular page 455, Figure 1, exemplifying 9 receptors with known ligands). Thus, these publications demonstrate that a number of ligand/receptors binding pairs with diverse structures were known in the art at the time of filing of the application.

Regarding the alleged unpredictability of adding tags to ligands, the Office Action cites an article by Janda (Proc. Natl. Acad. Sci. USA 91:10779-10785 (1994)) as describing the unpredictability of tagging methods. However, the article by Janda cites several references that have successfully used different tagging methods. These methods include diverse tagging strategies such as phage display, a "peptides on plasmids" method by Affymax, a peptide coded library method by Chiron Corporation, electrophoric tagging, and encoded combinatorial libraries. Thus, Janda supports the teachings in the specification that one skilled in the art would expect to successfully tag a ligand variant population without undue experimentation.

The Office Action alleges that no working examples of the claimed methods where the receptors are tagged, especially with respect to imparting and decoding the information present in an identifiable tag, are provided. As discussed above, a working

example is not required and the requirement is that the specification provides sufficient disclosure to teach those of ordinary skill how to make and use the invention as claimed. In regard to tagging ligands, the specification teaches methods of tagging variants (page 28, line 28, through page 30, lines 24). Methods for detecting the tag, for example using antibodies specific for the peptides in FACS analysis, are also described on page 30, lines 8-20. The specification also teaches methods for tagging a variant by co-expression of a peptide tag on the parental expression vector (Example I on page 38, lines 18-33). Therefore, Applicants respectfully submit that the specification provides sufficient description for how to tag with an identifiable tag.

Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed methods. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 5 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for use of the word "optimal" in reference to optimal binding activity.

Applicants submit that the meaning of the term "optimal" as most desirable or favorable would be known by one skilled in the art. In addition, the specification provides sufficient description and guidance for the meaning of the term

"optimal" in reference to binding activity because the specification teaches that "optimal binding" is a preferred binding characteristic of a ligand and receptor interaction, and can be ligand-receptor interactions of a desired affinity, avidity or specificity (page 10, lines 23-27). Exemplary optimal binding characteristics such as binding affinity, binding to the largest number of variants or binding to greater than some threshold number of variants are also provided in the specification, for example, at page 10, line 27, through page 11, line 14.

Applicants respectfully submit that the specification provides sufficient description and guidance for the meaning of the term "optimal" in reference to binding activity. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-8 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Lerner et al. (U.S. Patent No. 5,462,856; on PTO-1449). The Office Action alleges that Lerner et al. discloses a method for identifying a chemical that acts as an agonist for a GPCR. In addition, the Office Action alleges that Lerner et al. teach cloning new GPCRs that reads on the claimed collective receptor variant populations, and teach bioassays that read on the contacting and detecting steps of the claimed methods. The Office Action further alleges that Lerner et al. disclose a procedure where clones are subdivided into

smaller pools that reads on the dividing, contacting and detecting steps of the claimed methods.

Applicants respectfully submit that the claims are novel over the Lerner et al. patent. The claims are directed to methods for determining binding of a receptor to one or more ligands by contacting a collective receptor variant population with one or more ligands and detecting binding of the one or more ligands to the collective receptor variant population. Lerner et al. does not teach a collective receptor variant population. At best, the Lerner et al. patent merely describes the cloning of GPCRs in the melanophore system using random cDNA libraries. In contrast, the subject specification teaches the use of a collective receptor variant population and not random cDNA libraries. For example, the specification describes variations of a parent receptor that can make up a collective receptor variant population (see, for example, page 8, line 26, to page 9, line 25). Thus, the Lerner et al. reference does not teach each element of the claimed invention and, therefore, it cannot anticipate the claimed invention. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The

Examiner is invited to contact the undersigned agent or Cathryn Campbell with any questions in regard to this application.

Respectfully submitted,

May 19, 2003
Date

Deborah L. Cadena
Registration No. 44,048
Telephone No. (858) 535-9001
Facsimile No. (858) 535-8949

MCDERMOTT, WILL & EMERY
4370 La Jolla Village Drive
7th Floor
San Diego, California 92122

Inventors: Huse and Freedman
Serial No.: 09/839,469
Filed: April 20, 2001

APPENDIX A

In the Specification:

Please delete the paragraph on page 54, line 17 through page 55, line 12 and substitute therefor:

The results of the screen are summarized in Figure [6] 4, where receptors are represented as discs and ligands are represented as symbols. These results demonstrate that screening ligands against a population of receptor variants will rapidly identify ligands having optimal binding activity. For example, if the collective receptor variant population of this example were screened in the melanophore system, ligand No. 3 would have generated the highest signal since it binds to all seven receptors in the receptor variant population. Ligand No. 7 would give a weaker signal since this ligand binds to three receptors in the receptor variant population. Ligand No. 1 would give a still weaker signal since this ligand binds to two receptors in the receptor variant population. Thus, screening with a collective receptor variant population provides more information about the binding characteristics of the ligand than screening with the parent receptor alone. In addition, ligands that bind weakly to the parent receptor may not have been detectable above background when screened against the parent alone but are detectable when more than one receptor in the receptor variant population binds to the ligand.

Please delete the table on page 53, lines 1-18, and substitute therefor:

Table I. Nucleotide and Amino Acid Sequences of Receptor Variants of BR96 Antibody

CDR L1

[CDR L1]	Amino Acid SEQ ID NO:	26	27	28	29	30	31	32	33
1	Wild type	AGC	TCA	AGT	GTA	AGT	TTC	ATG	AAC
2		Ser	Ser	Ser	Val	Ser	Phe	Met	Asn
3	M131B3-5	AGC	TCA	AGT	GTA	**AGG**	TTC	ATG	AAC
4		Ser	Ser	Ser	Val	**Arg**	Phe	Met	Asn
5	M131B3-6	AGC	**GAG**	AGT	GTA	**AAT**	**CTT**	ATG	AAC
6		Ser	**Glu**	Ser	Val	**Asn**	**Leu**	Met	Asn
7	M131B3-7	AGC	TCA	AGT	GTT	**AAT**	TTC	ATG	AAC
8		Ser	Ser	Ser	Val	**Asn**	Phe	Met	Asn
9	M131B3-10	AGC	TCA	**ACG**	GTA	AGT	TTC	ATG	AAC
10		Ser	Ser	**Thr**	Val	Ser	Phe	Met	Asn
11	M131B3-11	AGC	TCA	AGT	GTA	**GCG**	**TAT**	ATG	AAC
12		Ser	Ser	Ser	Val	**Ala**	**Tyr**	Met	Asn
13	M131B3-12	AGC	**CAG**	AGT	**GCT**	**AAG**	**CAT**	ATG	AAC
14		Ser	**Gln**	Ser	**Ala**	**Lys**	**His**	Met	Asn

Please delete the table on page 54, lines 1-16, and substitute therefor:

CDR L2

[CDR L2]	Amino Acid SEQ ID NO:	49	50	51	52	53	54	55	56
15	Wild type	GCC	ACA	TCC	AAT	TTG	GCT	TCT	GGA
16		Ala	Thr	Ser	Asn	Leu	Ala	Ser	Gly
17	M131B3-5	GCC	ACA	**GAG**	**AAG**	TTG	GCT	TCT	GGA
18		Ala	Thr	**Glu**	**Lys**	Leu	Ala	Ser	Gly
19	M131B3-6	GCC	ACA	**GTT**	AAT	TTG	GCT	TCT	GGA
20		Ala	Thr	**Val**	Asn	Leu	Ala	Ser	Gly
21	M131B3-7	GCC	ACA	**GTG**	AAT	TTG	GCT	TCT	GGA
22		Ala	Thr	**Val**	Asn	Leu	Ala	Ser	Gly
23	M131B3-10	GCC	ACA	TCC	**AGG**	**GCG**	GCT	TCT	GGA
24		Ala	Thr	Ser	**Arg**	**Ala**	Ala	Ser	Gly
25	M131B3-11	GCC	ACA	**CAG**	AAT	TTG	GCT	TCT	GGA
26		Ala	Thr	**Gln**	Asn	Leu	Ala	Ser	Gly
27	M131B3-12	GCC	ACA	TCC	AAT	TTG	GCT	TCT	GGA
28		Ala	Thr	Ser	Asn	Leu	Ala	Ser	Gly